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MAIL STOP - PCT
Docket No.: 27705U

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor: BUHR
Appl. No.: 10/578,801
Appl. Filing Date: October 18, 2006
Intl. Appl. No.: PCT/EP2005/051822
Intl. Appl. Filing Date: April 22, 2005

Art Unit: XX
Examiner: XX
Confirm. No.: XX

For: **6,7-DIHYDROXY-8-PHENYL-3,6,7,8-TETRAHYDRO-CHROMENO[7,8-D]IMIDAZOLE DERIVATIVES AND THEIR USE AS GASTRIC ACID SECRETION INHIBITORS**

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Submitted herewith for filing in the U.S. Patent and Trademark Office is the following:

1. Submission of Documents to Supplement Filing Documents under 35 USC 371;
2. PCT/IB/373 (International Preliminary Report on Patentability); and
3. PCT/ISA/237 (Written Opinion of the International Searching Authority).

The Commissioner is hereby authorized to charge any deficiency or credit any excess to Deposit Account Number 14-0112.

Respectfully submitted,
NATH & ASSOCIATES PLLC

December 4, 2006

Gary M. Nath, Reg. No. 26,965
Sheldon M. McGee, Reg. No. 50,454
Customer No. 34375

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SUBMISSION OF DOCUMENTS TO SUPPLEMENT FILING DOCUMENTS UNDER 35 USC 371

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In order to supplement the filing documents for the national phase filing Under USC 371 commenced on October 18, 2006, applicant now submits the following documents:

1. PCT/IB/373 (International Preliminary Report on Patentability); and
2. PCT/ISA/237 (Written Opinion of the International Searching Authority).

Please charge any deficiency or credit any overpayment to our Deposit Account Number 14-0112.

Respectfully submitted,
NATH & ASSOCIATES PLLC

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 1294WOORD01	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/EP2005/051822	International filing date *(day/month/year)* 22 April 2005 (22.04.2005)	Priority date *(day/month/year)* 26 April 2004 (26.04.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ALTANA PHARMA AG		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 01 November 2006 (01.11.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Ellen Moyse e-mail: pt05@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

REC'D 30 AUG 2005
WIPO PCT

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

3/11

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/051822	22.04.2005	26.04.2004

International Patent Classification (IPC) or both national classification and IPC
C07D491/04, C07D491/14, A61K31/4188

Applicant
ALTANA PHARMA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
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Authorized Officer

Fink, D

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/051822

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 12 (as regards industrial applicability)

because:

☒ the said international application, or the said claims Nos. 12 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/051822

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	2, 6, 8, 10
	No:	Claims	1, 3-5, 7, 9, 11, 12
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III.

The present **claim 12** relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.
Consequently, no opinion will be formulated with respect to industrial applicability of the subject-matter of this claim.

[For the assessment of the aforesaid claim on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a (known) *compound for* first *use in medical treatment* and the *use* of such a compound *for the manufacture of a medicament* for a new medical treatment.]

Re Item V.

The following documents (D) are considered to be relevant:

D1: ..... EP-A-0266326 (7 August 1997);
D2: ..... WO-A-01/72755 (4 October 2001);
D3: ..... WO-A-2004/087701 (***14 October 2004***);
D4: ..... WO-A-03/014123 (20 February 2003);
D5: ..... WO-A-98/54188 (3 December 1998);

1. NOVELTY (Article 33(2) PCT):

The present application satisfies the criterion set forth in Article 33(2) PCT because the subject-matter of **claims 1-12** is new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT):

The compounds of present **claim 1** are novel over the prior art **D1**, **D2**, **D4** and **D5** on account of the *3,6,7,8-tetrahydro-**chromeno[7,8-d]imidazole*** ring system (cf., the *4-benzyloxy*-benzimidazole derivatives according to claim 1 of **D1**; and the 7-H-8,9-dihydro-pyrano[2,3c]*imidazo[1,2-a]pyridine* derivatives according to the first claims of **D2**, **D4** and **D5**).

The compounds of present **claim 1** are furthermore novel over the prior art **D3** (published on ***14 October 2004***) on account of the ***oxy*** substituents attached to positions 6 and 7 of the 3,6,7,8-tetrahydro-chromeno[7,8-d]imidazole ring system (cf., the present substituent groups R3-***O***- and R4-***O***- and the 6,7- *unsubstituted* 3,6,7,8-tetrahydro-chromeno[7,8-d]imidazole ring system according to claim 1 of **D3**).

2. INVENTIVE STEP (Article 33(3) PCT):

The present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of **claims 1, 3-5, 7, 9, 11** and **12** does not appear to involve an inventive step (Rule 65(1)(2) PCT):

2.1. It would appear that the present **claims 2, 6, 8** and **10** are **fully entitled** to the presently claimed **first** priority date of ***26.04.2004***.

Accordingly, the document **D3** - which is published on ***14.10.2004*** - may not be taken into account for the assessment of the question of inventive step of these claims.

The compounds of the present **claims 2, 6, 8** and **10 differ** from the compounds of **D1**, **D2**, **D4** and **D5** in that they are *3,6,7,8-tetrahydro-**chromeno[7,8-d]imidazole*** derivatives rather than *4-benzyloxy*-benzimidazole derivatives (cf., **D1**) and 7-H-8,9-dihydro-pyrano[2,3c]*imidazo[1,2-a]pyridine* derivatives (cf., **D2**, **D4** and **D5**), respectively.

In the light of this prior art the **problem** to be solved by the compounds of the present n **claims 2, 6, 8** and **10** resides in the provision of <u>further</u> benzimidazole derivatives having *gastric acid secretion inhibitory* activity.

The said problem has been **solved** by the compounds of the present **claims 2, 6, 8** and **10** (cf., the activity data (*gastric acid secretion inhibition*) of the table A on page 16 of the present description).

Given the fact that none of the available prior art documents suggests *3,6,7,8-tetrahydro-**chromeno[7,8-d]imidazole*** derivatives for the said use (**D1** is silent in respect of a *3,6,7,8-tetrahydro-chromeno[7,8-d]*imidazole ring system; and **D2**, **D4** and **D5** relate to *imidazo[1,2-a]pyridine* derivatives rather than *benzimidazole* derivatives), it is considered that the present solution (i.e., the compounds of the present **claims 2, 6, 8** and **10** may be regarded to be **non-obvious** in the sense of Article 33(3) PCT.

It is therefore considered that the subject-matter of the present **claims 2, 6, 8** and **10** involves an inventive step as set forth in Article 33(3) PCT.

2.2. It would furthermore appear that the present **claims 1, 3-5, 7, 9, 11** and **12** are **only entitled** to the present filing date of ***22.04.2005***.

Accordingly, the document **D3** - which is published on ***14.10.2004*** - is considered to represent state of the art in the sense of Article 33(3) PCT.

The compounds of the present **claims 1, 3-5, 7** and **9 differ** from the *gastric acid secretion inhibitors* of their **closest prior art D3** essentially only in that they have ***oxy*** groups attached to positions 6 and 7 of the 3,6,7,8-tetrahydro-chromeno[7,8-d]imidazole ring system (cf., the present substituent groups R3-***O***- and R4-***O***- and the 6,7- *unsubstituted* 3,6,7,8-tetrahydro-chromeno[7,8-d]imidazole ring system according to claim 1 of **D3**). More specifically, **D3** discloses e.g. the compound 2,3-Dimethyl-8-phenyl-3,6,7,8-tetrahydro-chromeno[7,8-d]imidazole (cf., page 35, example 36).

In the light of **D3** the **problem** to be solved by the compounds of the present **claims 1, 3-5, 7** and **9** resides in the provision of <u>further</u> 8-phenyl-3,6,7,8-tetrahydro-chromeno[7,8-d]imidazole derivatives having *gastric acid secretion inhibitory* activity.

The said problem has been **solved** by the compounds of the present **claims 1, 3-5, 7** and **9** (cf., the activity data (*gastric acid secretion inhibition*) of the table A on page 16 of the present description).

Having regard to the prior art **D2** - **D4**, it is considered that the present solution does not appear to involve an inventive step for the following reasons:

1. It is known from **D3** that 8-phenyl-3,6,7,8-tetrahydro-***chromeno[7,8-d]imidazole*** derivatives such as the 2,3-Dimethyl-8-phenyl-3,6,7,8-tetrahydro-chromeno[7,8-d]imidazole of the example 36 possess *gastric acid secretion inhibitory* activity;

2. it is further known that 8-phenyl-3,6,7,8-tetrahydro-***chromeno[7,8-d]imidazole*** (cf., **D3**) **as well as** 9-phenyl-7-H-8,9-dihydro-pyrano[2,3c]***imidazo[1,2-a]pyridine*** derivatives (cf., **D2**, **D4** and **D5**) possess *gastric acid secretion inhibitory* activity (see, for instance, the table A of **D3** according to which e.g.

the compound 2,3-Dimethyl-8-phenyl-3,6,7,8-tetrahydro-chromeno[7,8-d]imidazole(+/-)-*5-carboxylic acid dimethylamide* (compound 1) *inhibits gastric acid secretion*: > ***50%*** (at *1.0 µmol/kg*) , and

the table A of **D4** according to which e.g.

the compound 2,3-Dimethyl-9-phenyl-7-H-8,9-dihydro-pyrano[2,3c]imidazo[1,2-a]pyridine-*6-(N,N-dimethyl)carbamide* (compound 3) *inhibits gastric acid secretion*: ***100%*** (at *3.0 µmol/kg*)); and

3. it is known that *7,8-unsubstituted 9*-phenyl-7-H-8,9-dihydro-pyrano[2,3c]*imidazo-[1,2-a]pyridine* (cf., **D4**) **as well as** ***7,8-hydroxy***-9-phenyl-7-H-8,9-dihydro-pyrano[2,3c]-*imidazo[1,2-a]pyridine* derivatives (cf., **D2** and **D5**) show *gastric acid secretion inhibitory* activity.

Accordingly, the person skilled in the art would have expected that the accordingly modified compounds of **D3** (cf., for instance, the compound 2,3-Dimethyl-8-phenyl-3,6,7,8-tetrahydro-*chromeno[7,8-d]imidazole* of the example 36 of **D3** and the corresponding compound ***6,7-Dihydroxy***-2,3-dimethyl-8-phenyl-3,6,7,8-tetrahydro-*chromeno[7,8-d]imidazole* according to the present **claim 1**) would display (some) *PDE4 inhibitory* activity.

It is therefore considered that - in the absence of any ***unexpected / surprising effect*** - the compounds of the present **claims 1, 3-5, 7, 9, 11** and **12** have to be regarded to be **obvious** in the light of the teaching of **D1** and **D3**.

3. INDUSTRIAL APPLICABILITY (Article 33(4) PCT):

The subject-matter of the present **claims 1-11** concerns chemical compounds and a pharmaceutical composition and is therefore considered to be industrial applicable in the sense of Article 33(4) PCT.